ARTICLE

Evaluation of antiparkinsonian drugs in pharmacy records as a marker for Parkinson's disease

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Abstract
Aim: The aim of this study was to determine whether use of antiparkinsonian drugs in pharmacy records can be used as a marker for patients with Parkinson's disease (PD).
Method: Data were obtained from the Rotterdam Study, a community-based prospective cohort study among people aged 55 years or older who were all screened for PD. For 5510 persons, of whom 74 had PD, pharmacy records were available. Stepwise logistic regression analysis was used to evaluate whether age, sex and use of the antiparkinsonian drugs amantadine, anticholinergics, dopamine agonists, levodopa and selegiline, were predictive variables for PD. For each individual a probability for having PD was calculated. Sensitivity, specificity and positive predictive value (PPV) were calculated at different cut-off values based on calculated probabilities.
Results: More than 90% of the users of levodopa, bromocriptine, selegiline, and users of at least two different antiparkinsonian drugs had PD. Age, use of amantadine, anticholinergics, bromocriptine, levodopa, and selegiline were predictive variables for PD. After application of different cut-off values, sensitivity was at most 66.2%, and specificity was at least 99.8%. A PPV of higher than 90% was obtained at higher probabilities.
Conclusion: Based on the high PPV of our predictive model, antiparkinsonian drugs can be used as a reliable marker for PD in pharmacy records. Because sensitivity is low, pharmacy records cannot be used to estimate prevalence of PD.

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Introduction

Pharmacy records are a reliable source of drug exposure [1,2]. They offer an easy and inexpensive way to collect drug exposure information for large numbers of patients. These records are therefore widely used in pharmacoepidemiological research [3-5]. We have started a project to study the quality of pharmacotherapy and the frequency of Parkinson's disease (PD) using pharmacy records. Antiparkinsonian drugs are important for the treatment of PD [6]. Use of these drugs may therefore be considered as marker for PD in pharmacy records. However, antiparkinsonian drugs have indications other than PD, e.g. anticholinergics are used for treatment of dystonia. It is therefore important to evaluate whether antiparkinsonian drugs are used specifically by patients with PD. Furthermore, not all patients with PD are treated pharmacologically [7]. To estimate the prevalence, it should be known what proportion of patients are treated with antiparkinsonian drugs.

Other studies, that have evaluated whether the use of antiparkinsonian drugs is specific for PD, had limitations [8-10]. First, levodopa [8,9], or levodopa and selegiline [10], were taken as only marker for PD. Other antiparkinsonian drugs can also be used for treatment of PD [6]. A recent population-based study found that only 41% of patients with PD used levodopa [11]. Therefore, previous studies did not identify all patients with PD treated with antiparkinsonian drugs. Second, previous studies compared pharmacy records with medical records [8-10]. Medical records will miss patients who have not been diagnosed (yet) [12]. A better approach is to compare pharmacy records with data from a population-based study. In such a study, all persons are examined for signs of PD and all patients are diagnosed with use of the same diagnostic criteria.

The aim of our study was to determine whether antiparkinsonian drugs can be used as a marker for PD in pharmacy records. We also wanted to determine how many patients were missed in pharmacy records because they were not treated pharmacologically.

Methods

Data

Data were obtained from the first cross-sectional survey of the Rotterdam Study, a population based prospective cohort study on prevalence, incidence, and determinants of diseases in the elderly. The study population comprised inhabitants of Ommoord, a suburb of Rotterdam, aged 55 years and older [14]. Between 1990 and June 1993, 7983 persons agreed to participate and signed informed consent statements. All participants were interviewed at home and most were subsequently examined at a research center. Of these 7983 persons, only 7129 visited the research center. This slight decrease can be ascribed to refusal, disease, or death of the participants. For this study we used the 6969 subjects who had a neurological screening examination [7]. Prescription data of subjects were obtained from all three community pharmacies in Ommoord and were available for the period between January 1, 1991 and December 31, 1997. In the Netherlands, pharmacy records are virtually complete [1] and antiparkinsonian drugs are fully reimbursed. Pharmacy records contain patient's date of birth, and gender. They include the name of each prescription drug a person is using, the date of dispensing, dosage, number of units, and duration.

Definitions

In our definition, a person had PD if at least two of the cardinal signs (i.e. resting tremor, rigidity, bradykinesia, or impaired postural reflexes) were present, either

at the physical examination or in medical history, and if there was no other cause of parkinsonism. Examinations were made by a neurologist-in-training or a neurologist. All newly diagnosed patients were reevaluated by a second neurologist [7].

The antiparkinsonian drugs in our study were amantadine, anticholinergic drugs (biperidene, dexetimide, orphenadrine, procyclidine, trihexifenidyl), dopamine agonists (bromocriptine, lisuride, pergolide), levodopa (with or without a decarboxylase inhibitor), and selegiline. A person was defined as user if the examination date was between the dispensing date and the discontinuation date of a prescription for an antiparkinsonian drug. The discontinuation date was the dispensing date plus the period equal to the total number of dispensed tablets divided by the number prescribed per day. We arbitrarily multiplied this period by 1.1 to control for residual drug effects and irregular use of medication.

Exclusion criteria

Pharmacy records were not available before 1991. In the Netherlands, prescription drugs are dispensed for a maximum of 90 days. Therefore, we have excluded patients who had the neurological screening examination before April 1, 1991. People who did not fill any prescription in the study area may have purchased prescription drugs elsewhere and were excluded.

Analysis

We calculated the proportion of patients with PD among users of a certain antiparkinsonian drug.

Stepwise multivariate logistic regression analysis was used to evaluate whether age (per year), sex and use of the antiparkinsonian drugs amantadine, anticholinergics, dopamine agonists, levodopa and selegiline were associated with PD. Interaction between these variables was also studied. The coefficients of the selected variables were used to calculate a probability for each individual of having PD. This probability was calculated using the formula $e^x / (1+e^x)$, in which x is the sum of the constant and different product terms of coefficients and variables which were selected in the logistic model. Subsequently, at probabilities with an increment of 0.1, it was determined how many people were correctly and incorrectly classified as having PD. Sensitivity (i.e. proportion of people with PD correctly classified as such), specificity (i.e. proportion of people without PD correctly classified as such), positive predictive value (PPV, i.e. proportion of people who have a probability of at least a given value and who have PD) were computed at different probabilities. Sensitivity is the most important measure to determine whether pharmacy records can be used to study prevalence of PD. PPV is the relevant measure to estimate whether antiparkinsonian drugs can be used as a marker for PD in pharmacy records.

A receiver operator characteristic (ROC) curve was drawn through plotting of 100% minus specificity on the horizontal axis and sensitivity on the vertical axis. The accuracy of the ROC is given by the area under the curve (AUC). Contrary to sensitivity and specificity, this area is not dependent on arbitrarily chosen probabilities. The area is the probability that results are correctly classified, given one person with PD and one person without PD. AUC ranges from 0.5 (no apparent accuracy) to 1.0 (perfect accuracy). The AUC was calculated through the trapezoidal rule [15].

Results

Of the 6969 subjects who have had the neurological screening examination, 5510 persons were eligible of whom 74 had PD. We have excluded 1282 subjects (19 persons with PD), because they were examined before April 1, 1991. Another 177 subjects (four with PD) were not considered, because they did not fill a prescription in one of the community pharmacies of Ommoord. Of the 74 eligible patients with PD, 11 were diagnosed as such for the first time in the survey. Table 1 shows the age and sex distribution of the study population and the number and percentage of persons with PD.

Table 2 lists the number of users of antiparkinsonian drugs with and without PD. Sixty-three subjects were defined as users of an antiparkinsonian drug, 49 of these persons had PD. The most common treatment was levodopa. All users of selegiline were defined as having PD. Bromocriptine was the only dopamine agonist in use. All subjects who used at least two different antiparkinsonian drugs had PD. None of the newly diagnosed patients used antiparkinsonian drugs. The proportion of users of an antiparkinsonian drug that had PD, ranged from 43% for anticholinergics, to 100% for selegiline. More than 90% of the users of bromocriptine and levodopa had PD.

Stepwise multivariate logistic regression analysis showed that age, amantadine, anticholinergics, bromocriptine, levodopa and selegiline were associated with PD. (Table 3) Sex and interaction terms were not selected by the stepwise multivariate logistic regression analysis. The probability for an individual of 55 years or older of having PD is therefore:

$$e^x / (1 + e^x)$$

In which:

$$x = -13.054 + 0.10*age + 6.08*amantadine + 3.76*anticholinergics + 5.62*bromocriptine + 6.51*levodopa+13.22*selegiline$$

In this formula, patients who use a certain drug are given a value of one, and patients who do not use that drug a value of zero.

The p-value for use of selegiline appeared to be high (0.46), because this drug was only used by patients with PD. The coefficient of selegiline was therefore divided by zero. This means that the value listed in Table 3 (13.22) is an underestimation of the real measure, which is infinite. The value of 13.22 was arrived at, because at that point the maximum likelihood was reached and the iteration process stopped. The underestimated coefficient of selegiline is so high that for any patient using the drug a probability of almost 1.0 will be found.

Table 4 compares the outcome of our predictive model (predicted PD) with the gold standard (observed PD). If the probability of a patient of having PD as calculated by our logistic model was increased from at least 0.1 to at least 0.9, sensitivity decreased from 66.2% to 45.9%, specificity was at least 99.8%, and PPV increased from 80.3% to 100%. Users of at

Table 1 *Age and sex distribution of the study population and the number and percentage of persons with Parkinson's disease (PD)*

Age (years)	Men total	PD	Women total	PD	Total total	PD
55-64	908	3 (0.3%)	1192	3 (0.3%)	2100	6 (0.3%)
65-74	868	11 (1.3%)	1079	9 (0.8%)	1947	20 (1.0%)
75-84	396	12 (3.0%)	717	24 (3.3%)	1113	36 (3.2%)
85-94	74	1 (1.4%)	257	10 (3.9%)	331	11 (3.3%)
95+	1	0	18	1 (5.6%)	19	1 (5.3%)
Total	2247	27 (1.2%)	3263	47 (1.4%)	5510	74 (1.3%)

Table 2 *Number and percentage of users of antiparkinsonian drugs on the date of examination, divided in patients with and without Parkinson's disease (PD)*

Antiparkinsonian drug	Users with PD	Users without PD	Total number of users
Amantadine	18 (86%)	3	21
Anticholinergics	6 (43%)	8	14
Bromocriptine	12 (92%)	1	13
Levodopa	33 (94%)	2	35
Selegiline	15 (100%)	0	15
At least two different antiparkinsonian drugs	25 (100%)	0	25
Total	49 (78%)	14	63

Table 3 *Results of stepwise multivariate logistic regression analysis, in which we studied whether age (per year), sex, and use of the antiparkinsonian drugs amantadine, dopamine agonists, levodopa, anticholinergics, and selegiline were associated with Parkinson's disease. Interaction terms were also evaluated in the model*

Variable*	Beta	SE	p
Age	0.10	0.02	<0.0001
Amantadine	6.08	0.83	<0.0001
Anticholinergics	3.76	0.86	<0.0001
Bromocriptine	5.62	1.21	<0.0001
Levodopa	6.51	0.84	<0.0001
Selegiline	13.22	18.01	0.46
Constant	-13.05	1.537	<0.0001

Model chi-square = 459.57; df=6; $p < 0.0001$
* sex and interaction terms were not included in the model

Table 4 *Distribution of the number of subjects that are classified correctly or incorrectly as having Parkinson's disease (PD) based on cut-off probabilities computed using the coefficients of Table 3 and corresponding sensitivity, specificity, and positive predictive value. Calculation of the probability is $e^x/(1+e^x)$ in which x is the sum of the constant (-13.05), and the coefficients of the antiparkinsonian drugs a subject is using (amantadine 6.08, anticholinergics 3.76, bromocriptine 5.62, levodopa 6.51, selegiline 13.22) and the product of age and coefficient of age (0.10)*

Probability[1]	According to gold standard PD (n=74)	Without PD (n=5436)	Se[2]	Sp[3]	PPV[4]
≥0.1	49	12	66.2%	99.8%	80.3%
≥0.2	48	10	64.9%	99.8%	82.8%
≥0.3	47	7	63.5%	99.9%	87.0%
≥0.4	47	6	63.5%	99.9%	90.4%
≥0.5	46	4	62.2%	99.9%	92.0%
≥0.6	46	4	62.2%	99.9%	92.0%
≥0.7	42	4	56.8%	99.9%	91.3%
≥0.8	40	1	54.1%	100.0%	97.6%
≥0.9	34	0	45.9%	100%	100%

[1]probability for having PD computed through stepwise multivariate logistic regression; [2]Se = sensitivity; [3]Sp = specificity; [4]PPV = positive predictive value

least two different antiparkinsonian drugs or selegiline had a probability of at least 0.9 (data not shown). Figure 1 presents the ROC curve. The AUC of 0.93 shows that pharmacy records can make an accurate classification of people with and without PD.

Discussion

We have found that use of antiparkinsonian drugs has a high PPV and is highly specific for PD in a population aged 55 years and older. However, sensitivity of antiparkinsonian drugs as a marker for PD is low, because approximately one in every three patients is not treated pharmacologically.

Because sensitivity is low, pharmacy records reveal an underestimation of the prevalence of PD and can therefore not be used for this purpose. For construction of a cohort of patients with PD in pharmacy records, PPV should be high. Therefore a high probability should be chosen.

The decision to start treatment with antiparkinsonian drugs in patients with PD depends on the level of functional impairment [6]. Therefore, the model presented in this paper, will only identify the more severely diseased individuals. By taking higher positive predictive values, one does not select only the most severely diseased individuals. The reason for this is that selegiline has a high coefficient and this antiparkinsonian drug is used in the early stages of the disease [6].

Any study on PD is complicated by misdiagnosis caused by similarities between PD and other parkinsonian syndromes [16]. Diagnostic criteria used in this study excluded most of these syndromes [7,16] and the same number of diseased individuals would have been found if the United Kingdom PD society brain bank diagnostic criteria were used in persons up to 90 years [16,17].

The estimate of sensitivity, specificity and PPV could be wrong, because we have excluded all persons who did not fill any prescription. Persons without PD who have been excluded due to non-filling of a prescription, were mostly younger subjects who probably did not use any medication. PPV is therefore not affected, but specificity must be higher. However, specificity is already almost 100%. The four persons with PD who did not fill a prescription were institutionalized and probably received medication from a supply within the institute they were living. If they had been included sensitivity and PPV would have been slightly higher.

Most previous models used only levodopa as tracer for PD [8,9]. Menniti-Ippolito et al. used a model that included not only levodopa, but also selegiline and duration of treatment with these agents [10]. Our study shows that other antiparkinsonian drugs can be used too. De Pedro-Cuesta et al. have reported a specificity of 98%, which is in range with our study. They have not reported sensitivity, but have assumed that 5-10% of patients with PD are not treated pharmacologically [9]. Studies that evaluated sensitivity have found values of 88% [8] and 84% [10]. We report a lower sensitivity, because we compared pharmacy records with results of a population-based study and not with medical records as the other studies did. Contrary to these other studies, we have been able to take into account patients with PD who had not come to medical attention yet. In our study, only 35 out of 74 persons with PD (45%) used levodopa. Although this estimate is lower than figures reported in studies based on medical records, which reported figures ranging between 76% and 97% [18,21], it is in accordance with the percentage of 41% reported in a population-based study [11].

The results from our study can only be used in a comparable setting. First, the population should be at least 55 years. In younger people specificity and PPV

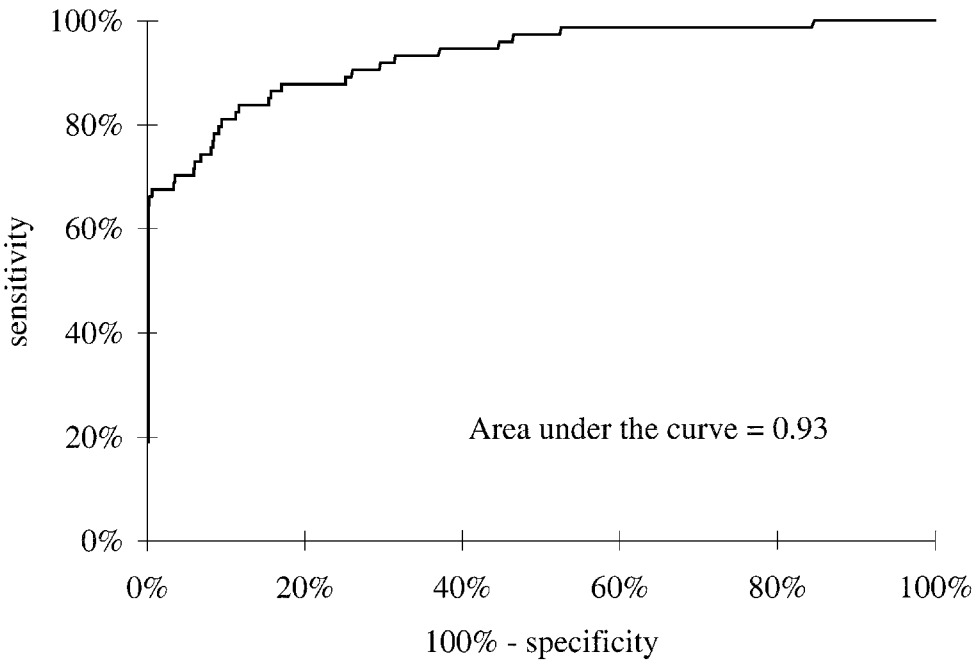

Figure 1

Receiver-operator characteristic curve (ROC) showing sensitivity versus 100%-specificity based on probabilities computed through stepwise logistic regression analysis for having Parkinson's disease (PD) for all 5436 subjects without PD and 74 subjects with PD

will be lower, since antiparkinsonian drugs are used to treat other disorders, for example bromocriptine for galactorrhea. Levodopa is used more conservatively in younger people, because of the long-term complications. Second, drug treatment should be similar. More physicians are active in a larger population and thus more combinations of drugs will be found. However, our study shows that any combination of antiparkinsonian drugs is used specifically by patients with PD. Third, the diagnosis should be made according to similar criteria. Fourth, data on drug use should be obtained from a source that contains all prescribed medications that an individual is taking.

This study shows that antiparkinsonian drugs in pharmacy records in patients aged 55 years and older are mainly used by patients with PD. Therefore, pharmacy records can be a useful tool for studying drug use in patients with PD that are treated with antiparkinsonian drugs. A prevalence estimate in pharmacy records will be hampered because approximately one in every three diseased individuals is not treated pharmacologically.

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